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EVALUATION OF SOME ANTIMOTION SICKNESS DRUGS ON THE SLOW ROTATION ROOM (NO. 1)

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JOINT REPORT

UNITED STATES NAVAL SCHOOL OF AVIATION MEDICINE

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EVALUATION OF SOME ANTIMOTION SICKNESS DRUGS ON THE SLOW ROTATION ROOM (NO. 1) *

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SUMMARY PAGE

THE PROBLEM

Fifteen young healthy subjects with normal semicircular canals based on the threshold caloric test were exposed to a total of 168 experimental trials in the Pensacola Slow Rotation Room under standardized conditions. One hour before each trial they received a capsule which contained either a placebo or drug. They were stressed to the point where definite symptoms of motion sickness appeared or until a cut-off point was reached.

FINDINGS

Of the antimotion sickness drugs tested, hyoscine proved to be the most effective. It was also observed that d-amphetamine was an effective antimotion sickness drug. The combination of hyoscine and d-amphetamine resulted in a supplemental therapeutic effect while most of the undesirable side effects of each drug were mutually eliminated. Meclizine was much less effective than either hyoscine or d-amphetamine, and no supplemental effect was seen when it was combined with d-amphetamine. Prochlorperazine was slightly effective but chlorpromazine, theithylperazine, and trimethobenzamide were ineffective.

It is emphasized that, before discussing the findings in detail, it should be clearly understood that: 1) they apply to a specific force environment and the degree to which extrapolation to other force environments can be made has yet to be investigated, and 2) the present study represents only a limited attempt to explore fully the efficacy of the drugs tested.

The advantages of the SRR in testing antimotion sickness drugs are pointed out.

INTRODUCTION

The antimotion sickness remedies have been studied in a wide variety of test situations, and sea and air transportation has provided the opportunity for carrying out several valuable studies (1, 5, 18). The difficulties, however, in maintaining constant test conditions due to changes in weather, position on board ship, and the posture of the subject have influenced some experimenters to use laboratory devices for their investigations. These devices include several types of swings (4), the vertical accelerator of Wendt (13), and the artificial waves used by Glaser's group (8) in England. These methods give standardized conditions which enable a more exact comparison of the effectiveness of the antimotion drugs. The incidental movements of the head, which are an important factor in motion sickness (14, 16), were not controlled in many of these experiments.

A series of experiments was performed at this laboratory using the Slow Rotation Room described in a previous report (11). In such a rotating environment whenever a person rotates his head about an axis other than that of the room, unusual patterns of angular accelerations are generated which stimulate the semicircular canals. At a given velocity of rotation of the room, experiment-paced head movements provide control of the stimulus, and other experimental conditions are readily standardized. It was the purpose of the present study to investigate the efficacy of certain antimotion sickness drugs in this unique force environment. The choice of drugs was based partly on the reports of other investigators (see ref. 19) who had used them under different conditions.

PROCEDURE

A group of fifteen healthy young male subjects comprised the test group in this study. Medical evaluation revealed no definite evidence of disease or disorder. None had a history of auricular disease, and caloric tests revealed a normal threshold response.

The major piece of equipment was the Pensacola Slow Rotation Room (SRR). This nearly circular, windowless room is mounted on the center platform of a human centrifuge, and rotation rates up to 20 RPM are feasible. The Dial Test (11) assured standardization of the subject's head movements by requiring him to set a pointer on each of a series of five dials. The dials were so arranged as to cause the subject to move his head and body through different complex arcs while the SRR was rotating. The order of the five dial settings was presented by a tape recorder with one setting every six seconds.

The subjects were given calibration runs in the SRR at increasing revolutions per minute (7.5 - 20) until on two successive runs the subject developed Malaise III within ten sequences of head movements. Diagnoses of motion sickness were made by an on-board, trained observer who utilized the diagnostic classifications which appear as Table I.

Table I

Important Vestibular Symptoms* Used in Diagnostic Categorization

Pathognomonic	Major	Minor	Diagnostic Terms
Vomiting	Retching		Vestibular Sickness: Vomiting or Two major symptoms or One major & two minor symptoms
	Nausea III or II	Nausea I	
	Increased Saliv. III or II	Increased Saliv. I	
	Pallor III	Pallor II	Malaise III:# One major symptom or Two minor symptoms or One minor & two other symptoms
	Cold Sweat III	Cold Sweat II	
	Drowsiness III	Drowsiness II	
			Malaise I: Any subjective symptom or Any sign usually associated with subjective symptom
			Malaise II: All other

* In rare instances other symptoms qualify.

Malaise III was used as an end point in the present study.

When the criteria of MAL III was reached on two successive runs, these data were averaged and considered to be the subject's "basal tolerance" for this condition. MAL III, rather than emesis, was used as an end point in order to avoid conditioning the subjects against the test and to maintain high motivation. This scale (Table I) of signs and symptoms enabled a definite and reliable diagnosis of motion sickness to be made.

Placebos were given on runs one, five, nine, and thirteen during the experiment to determine any shift in the baseline tolerance due to adaptation. When an active drug or placebo was given, a test session was terminated if the subject developed Malaise III or completed 300 head movements. The percentage increase of the head movements accomplished with an active drug over the baseline conditions (placebo) was taken as the effectiveness of that drug.

The drugs and doses used in this experiment are as follows for all subjects:

Hyoscine (Scopolamine)	0.6 mgm
Meclizine (Bonamine)	50.0 mgm
d-Amphetamine (Dexadrine)	10.0 mgm
Thiethylperazine (Torecan)	10.0 mgm
Trimethobenzamide (Tigan)	250.0 mgm
Chlorpromazine (Thorazine)	25.0 mgm
Prochlorperazine (Compazine)	5.0 mgm

Combinations of hyoscine (0.6 mgm) plus d-amphetamine (10 mgm), and of meclizine (50 mgm) plus d-amphetamine (10 mgm) were also used.

The order of presentation of each drug was dictated by a Latin Square design wherein placebo trials were interspersed in order to monitor an habituation effect if present. In order to prevent identification by the subject or experimenter, placebo and double blind procedures were used throughout the experiments wherein matched, opaque, oral capsules were available for all preparations. Each experimental administration of a drug (or placebo) was spaced by at least forty-eight hours and in some cases seventy-two hours. Each subject completed the entire series of experimental trials.

All subjects ate a light breakfast on the days of the experiments. This breakfast consisted of milk, cereal, and a sweet roll. Coffee was not permitted; however, the subjects were allowed to smoke. The capsule containing drug or placebo was given to a subject one hour prior to the experimental stress. The subjects were carefully observed for their responses to the drugs during the experimental trial. In addition to the Motion Sickness Questionnaire (17) which was administered prior to the experimental conditions, the subjects completed a set of additional questionnaires on each test day. These forms assessed the fitness of the subject to be tested, as well as his responses to the experimental condition (SRR) and the drug per se (i.e., side effects).

RESULTS

As may be seen in Figures 1 and 2, the most effective drug in this study was hyoscine which increased the average tolerance of the subjects to the motion by 147 per cent.* D-amphetamine increased the tolerance by 70 per cent when used alone but when combined with hyoscine a 194 per cent increase in tolerance resulted. Meclizine when used alone produced an increase of 50 per cent; in combination with d-amphetamine tolerance was raised by 43 per cent. Chlorpromazine, trimethobenzamide, thiethylperazine, and prochlorperazine were not significantly effective over the placebo. Prochlorperazine was the most promising of this latter group, increasing the tolerance for motion by 25 per cent. The group data (Table II) indicate the over-all effectiveness of hyoscine in combination with d-amphetamine; it was the most effective drug for five subjects. Seven other subjects showed pronounced improvement with the combined drugs. Hyoscine alone was the most effective drug in five subjects and was significantly beneficial in four other subjects. D-amphetamine was the most effective in one subject and gave a significant improvement in seven others. Meclizine was the best drug in one subject and produced a definite increase in tolerance in four subjects. The combination of meclizine and d-amphetamine was most effective in two subjects with seven others showing improvement. Prochlorperazine produced a definite improvement in one subject and a slight improvement in three others. The remaining drugs were of slight benefit in only two of the subjects. One subject failed to respond to any of the medications.

Side effects observed with the preparations were as follows: Hyoscine caused the subjects to become drowsy and dizzy and produced a dry mouth. When d-amphetamine was given, the subjects became talkative, nervous, and restless. The combination of hyoscine and d-amphetamine appeared to relieve the above side effects except for the dry mouth. Meclizine produced few side effects and a minimal amount of drowsiness. The addition of d-amphetamine to meclizine caused the subjects to become more restless and talkative again. Minimal side effects were reported with the remaining drugs.

DISCUSSION

Before discussing the findings in detail it should be clearly understood that: 1) they apply to a specific force environment, and the degree to which extrapolation to other force environments can be made has yet to be investigated, and 2) the present study represents only a limited attempt to explore fully the efficacy of the drugs tested.

The most surprising finding was the effectiveness of d-amphetamine, a sympathomimetic drug. There are several earlier reports in the literature to support this observation. Blackham (2), Hill (12), and Keevil (15) reported it to be an effective remedy. Chinn

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*All percentages are expressed as increases in tolerance to motion provided by the drug as compared to the placebo.

Table II

Number of Subjects Responding to Each Drug and Extent of Their Response

Drug	Meclizine	Meclizine & d-Amphetamine	Hyoscine	Hyoscine & d-Amphetamine	d-Amphetamine	Torecan	Tigan	Thorazine	Compazine
Dose	50 mg	50 mg + 10 mg	0.6 mg	0.6 mg + 10 mg	10 mg	10 mg	250 mg	25 mg	5 mg
Most effective	1	2	5	5	1	0	0	0	0
Definite improvement	4	5	4	7	7	0	0	0	1
Slight improvement	3	4	3	2	6	2	2	2	3
No improvement	7	4	3	1	1	13	13	13	11

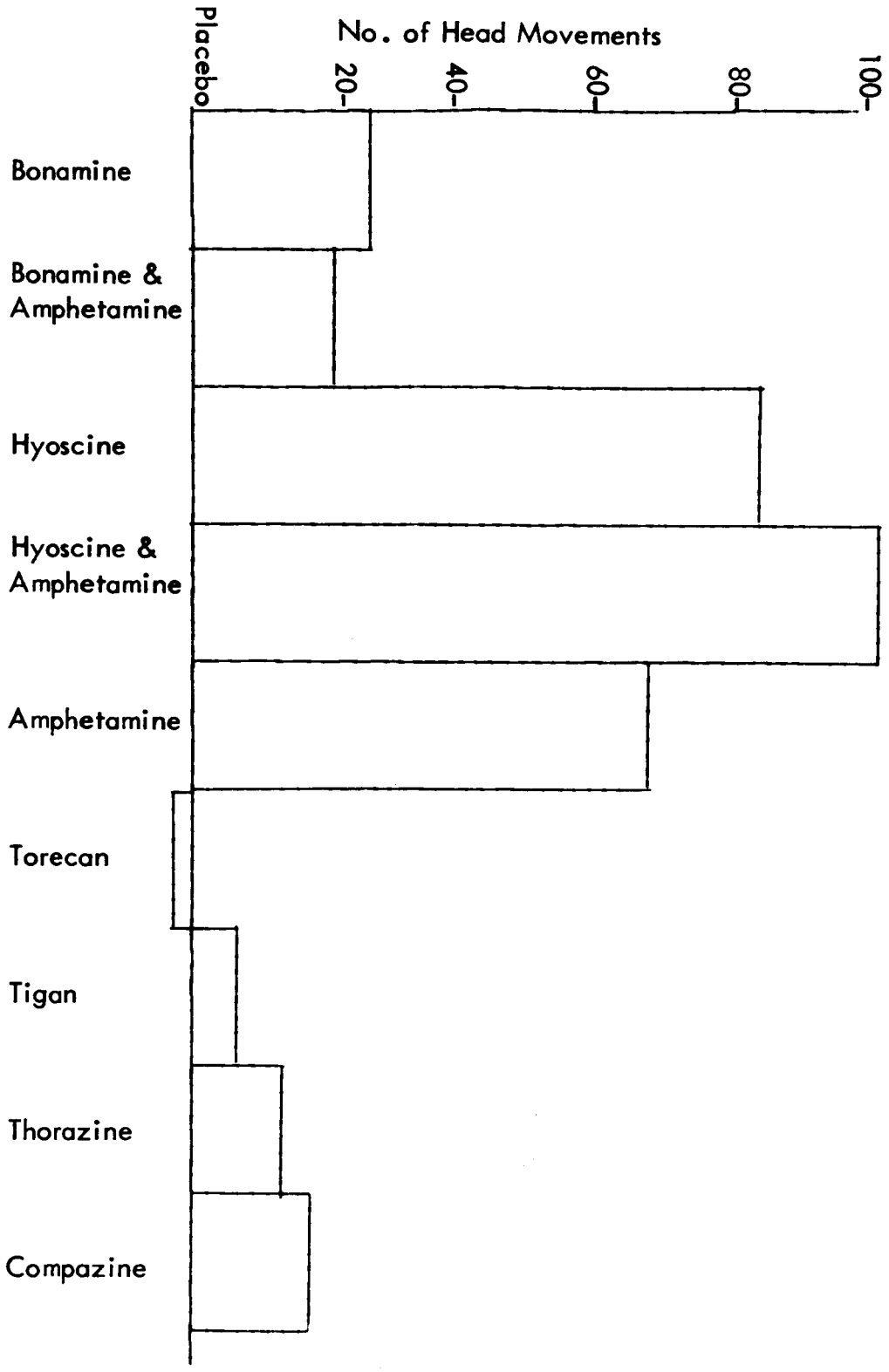

Figure 1

Increase in Number of Head Movements with Administration of Antimotion Sickness Drugs to Fifteen Men

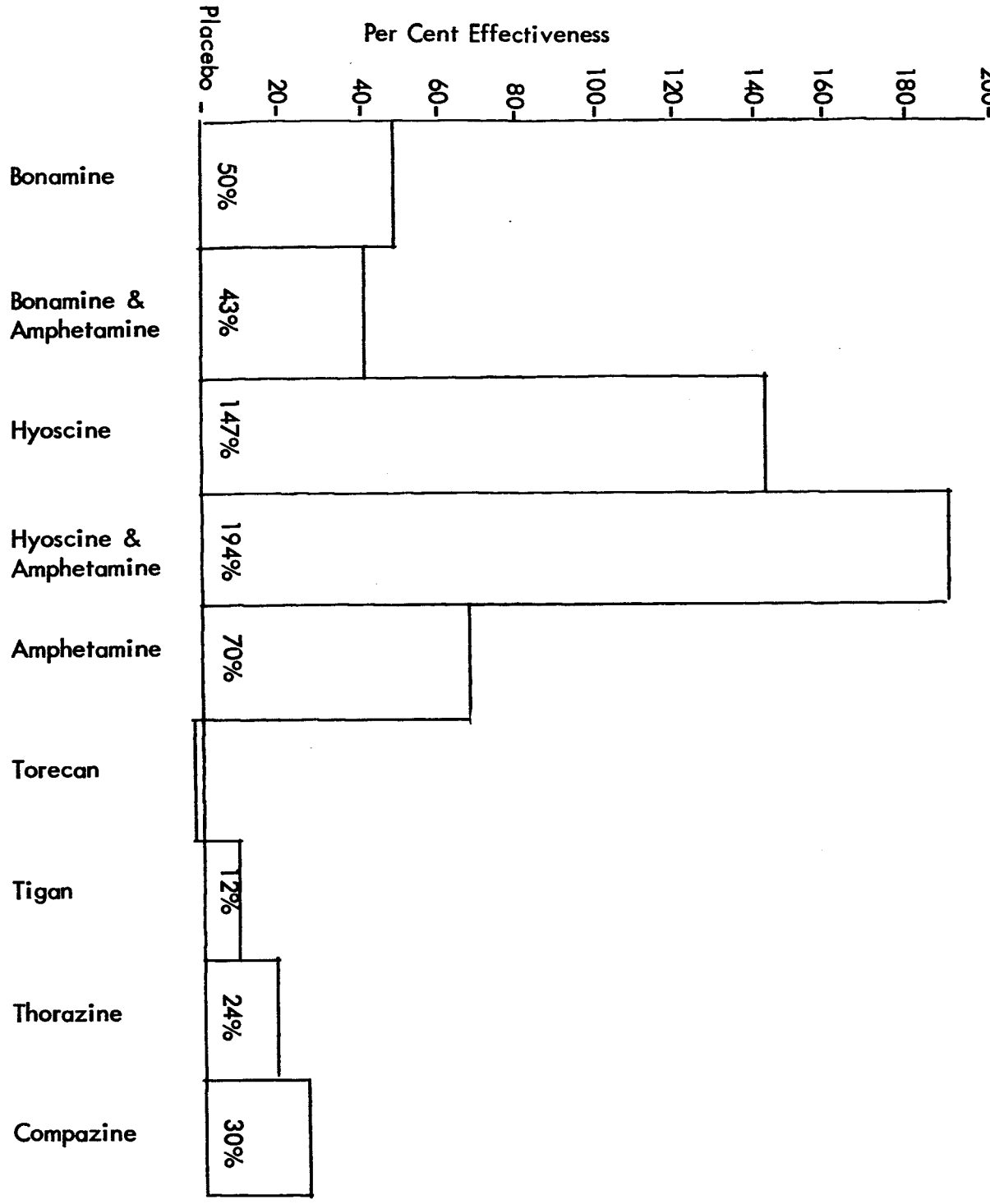

Figure 2

Percentage Effectiveness of the Antimotion Sickness Drugs for Fifteen Men

and Smith (4), however, reported it to be without effect in swing sickness. The action of d-amphetamine in preventing motion sickness cannot be explained either by depression of the vomiting center or of the central nervous system generally, both of which have been regarded as the effective mechanisms in the case of other drugs. Moreover, it would be difficult to attribute the efficacy of d-amphetamine in the present study to euphoria alone.

The British investigators (6 - 9) have long felt that hyoscine is the superior anti-motion sickness drug, while investigators in the United States (4,5) have favored the antihistamines as drugs of choice. In this study we found hyoscine to be definitely superior to meclizine. The side effects of hyoscine, such as the extreme drowsiness, however, would argue against its use by persons who had responsible duties to perform. The side effects of meclizine were much milder and should not interfere with duties of a routine nature. It was observed that d-amphetamine relieved most of the side effects of hyoscine and that a supplemental therapeutic effect was obtained. From a pharmacological standpoint it is quite appealing to discover two drugs which mutually relieve most of the side effects and give a supplemental therapeutic effect. Hyoscine which is a parasympatholytic and meclizine, although one of the antihistamines, have been reported to have some atropine-like action. The mechanisms of this group of drugs bring to mind the older theories of motion sickness (12) which were based on the observation that motion sickness symptomatology closely resembles over-activity of the parasympathetic nervous system. An overdose of physostigmine which produces an accumulation of acetylcholine, the transmitter substance of the parasympathetic system, brings about a similar set of symptoms. If an imbalance of the autonomic nervous system is part of the mechanism of motion sickness, then activation of the sympathetic or blocking acethylcholine in the parasympathetics could bring the system more nearly into balance and thus prevent the development of nausea.

A report (3) that D. F. P. (Di-isopropylfluorophosphate), which protects acetylcholine from breakdown, produces a nystagmus which is relieved only by eighth nerve section and various supporting studies would suggest that perhaps the antimotion sickness drugs act at the vestibular receptor sites, although a central action is also a possibility. The central nervous system depression following administration of these drugs would suggest a central mechanism such as depression of the vomiting center, although knowledge is insufficient at present to indicate any single site of action.

Trimethobenzamide has been shown to be a highly effective antiemetic in chemically induced nausea such as in toxic conditions and anesthesias. It was completely ineffective as an antimotion sickness preparation under the conditions of this study. A search of the literature fails to produce evidence that it has been sufficiently tested as an anti-motion sickness remedy.

A number of drugs that are potent antiemetics in chemically induced nausea (e.g., chlorpromazine) are not effective against motion sickness (4). That chlorpromazine is effective in some individuals may be attributed to its ability to relieve anxiety. It is

well-known that certain persons present an anxiety reaction rather than motion sickness per se (e.g., the proverbial sea voyager who becomes ill before going on board ship), and this drug may prove effective for these individuals. Further investigation of this drug is indicated before it can be fully accepted as an antimotion sickness preparation.

Thiethylperazine was also ineffective in this study. It is possible, however, that a higher dosage than that recommended at present will show it to be a useful drug.

A review of the current literature (19) concerning testing of antimotion sickness drugs reveals the use of a number of diverse test situations. The lack of a standard test stimulus has made it difficult to compare one drug with another in different studies and at times even within the same study. In addition, many studies do not report side effects or whether side effects were observed. In terms of the use of these drugs where responsible performance is critical, this shortcoming is significant. In some of the studies where laboratory techniques were utilized to test these drugs, the position of the head had not been controlled to eliminate random movements. The position of a man aboard ship, whether he is standing or reclining, and whether his head is stabilized or not have been shown to be of definite importance in the development of motion sickness (14, 16). These factors become increasingly important when studies on subjects with nonfunctioning vestibular mechanisms are studied since it has been reported that these subjects are immune to motion sickness even under the most extreme conditions (10). This would indicate that vestibular stimulation is the prime factor in motion sickness.

An attempt was made in the present study so that such conditions open to criticism would not exist. The subjects' familiarity with the SRR appeared to minimize some of the emotional factors usually encountered in motion sickness studies, although past conditioning remained an important factor. The strength of the stimulus with regard to the gravitoinertial force environment was quite well controlled, as were such factors as room temperature, relation to meals, and fitness of subjects. The use of a reliable end point well short of emesis represented a distinct advantage in that the subjects' motivation to participate in the entire experimental series was preserved. Definite signs and symptoms such as pallor, sweating, and stomach awareness appear long before the subject actually vomits (17). By carefully training observers to recognize these signs a definite end point was set up for this experiment, utilizing the standard established in previous research (10). Employing this end point permitted an intensive study of a highly selected group of subjects and a comparison of their individual responses to a series of drugs. In short, the Slow Rotation Room provides one of the best controlled conditions for testing these drugs that we now have available.

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A series of antimotion sickness drugs was evaluated on the human centrifuge at the Navy School of Aviation Medicine. The procedures used enabled the same stimulus to be applied to the individual subjects through the series of drug tests. A combination of hyoscine and d-amphetamine was found to be the most effective preparation. Hyoscine alone was the most effective single drug followed by d-amphetamine and meclizine Prochlorperazine was slightly effective, but chlorpromazine, thiethylperazine, and trimethobenzamide were ineffective. Hyoscine alone produced pronounced drowsiness. The combination with d-amphetamine relieved this side effect but not the vertigo and dry mouth. The advantages of the human centrifuge in the testing of antimotion sickness drugs are pointed out.

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